

REMARKS

Claims 1-16 have been cancelled. Claim 17 and 29 have been amended to more clearly define the ambit of protection sought, and to correct an obvious typographical error. Claims 18-22 and 25 have been amended to change claim dependency, and to clarify the ambit of protection sought. Claim 48 has been added to further clarify the ambit of protection sought. The specification has been amended to more accurately identify trademarks.

Specification

The Examiner has noted that trademarks should be capitalized and be accompanied by the generic terminology wherever they appear. Applicant has amended the specification accordingly.

Claim Rejections – 35 USC 102(b)

The Examiner has rejected claims 1-16, 18-20 and 22-28 as being anticipated by Mezei et al. (U.S. Patent No. 5,451,408). Solely in an effort to expedite prosecution, and by no means in acceptance of the Examiner's arguments, applicant has cancelled claims 1-16. Applicant reserves the right to resubmit these claims, for example, in a divisional application. Applicant has amended the claim dependency of claims 18-20 and 22, making these dependent from claim 17, rendering the Examiner's objections with regards to claims 18-20 and 22-28 moot.

Claim Rejections – 35 USC 103

The Examiner has objected to claims 17, 21, and 29-36 as unpatentable over Mezei et al (U.S. Patent No. 5,451,408).

The Examiner agrees that Mezei does not anticipate the claims cited, because Mezei lacks the explicit teaching of (a) a ratio of free fentanyl to liposomally encapsulated fentanyl of about 1:3; (b) a formulation consisting of alfentanil and morphine; and (c) a formulation containing alfentanil in a concentration from 300-6700 mcg/ml and morphine in a concentration of from 650-13350 mcg/ml.

However, the Examiner contends that it would have been obvious to a person of ordinary skill in the art at the time of the instant invention to modify the teachings of Mezei to utilize a ratio of about 1:3 of free fentanyl to liposomally encapsulated fentanyl, because Mezei's compositions inherently comprise free fentanyl and liposomally encapsulated fentanyl in a ratio ranging from 1:4 to about 1:9. The Examiner has stated that the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. The Examiner has stated that, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious.

Regarding the amounts of alfentanil and morphine, the Examiner contends that Mezei teaches exemplified compositions comprising 2,000 mcg/ml and 4000 mcg/ml, respectively, and that the motivation to combine alfentanil and morphine comes from the prior art.

Applicant respectfully traverses.

First, with respect to claim 17, Applicant has corrected an obvious clerical error, where a ratio of 3:1 was claimed instead of a ratio of 3:2. The ratio of 3:2 is properly supported in the description at paragraphs 0164, 0166, and elsewhere, including claim 21.

Further with respect to claim 17, applicant respectfully submits that unexpected results have been demonstrated from the claimed parameters, and that such results were never discussed, or even contemplated, in the prior art.

The selected ratios of liposomally encapsulated to free fentanyl allow for self-administration of the orally inhaled opioid formulation, with the ability to titrate to effect. This is taught throughout the specification, notably at Example 5, specifically, paragraphs 0168 to 0171, showing the clinical testing of the qualitative effects of the fentanyl preparations in human subjects. Applicant submits that this unexpected effect of the selected opioid formulations could not have been anticipated in the prior art, since titration to effect was not even contemplated. Although Mezei taught opioid formulations, in general, containing fentanyl and liposomally encapsulated fentanyl, many of these vast combinations of formulations would likely not be suitable for self-administration of opioids. Considerable inventive effort, as exemplified in both the pharmacokinetic modeling, and in the clinical examples shown in the present invention, was necessary to optimize the ratios of free to encapsulated fentanyl in order to provide the pharmacokinetic characteristics exemplified in the present invention. For example, an opioid formulation containing 10% free opioid, as taught in Mezei, would likely not have the required speed of onset of action required for self-titration to effect.

The selected and claimed ratios could not have been obvious in light of Mezei, since Mezei did not even present the problem of "titrating to effect", and patient self-administration of opioid, nor was Mezei attempting to overcome this problem.

Finally, the selected and claimed ratio could not have been obvious in light of Mezei, since the selected and claimed ratio is outside of the range taught by Mezei. Mezei taught a range of between 1:4 to about 1:9 (free:liposomally encapsulated), whereas the presently claimed composition is a ratio of about 2:3.

Applicant has amended claim 17 to specifically claim an opioid formulation for use in a method of providing analgesia to a patient in a pulmonary drug delivery device, wherein the formulation comprises free fentanyl and liposomally encapsulated fentanyl, wherein the ratio of concentration of liposomally encapsulated fentanyl to fentanyl is about 3:2. No new matter has been added by the present claim amendment.

Applicant has amended claim dependency in claims 18-22 and 25, with the result that claims 18-28 are now either directly or indirectly dependent on claim 17. As such, since claim 17 is not obvious (for the reasons stated above), it follows that claims 18-28 can not be obvious.

With respect to claim 29, applicant respectfully traverses. Although combinations of opioids may be known in the art generally, and a combination of free and encapsulated fentanyl is disclosed in Mezei, neither combinations of free and encapsulated opioid, for pulmonary delivery, nor a specific selection of alfentanil and morphine were not previously known in a composition suitable for pulmonary administration. The specific selection of alfentanil and morphine was also not obvious, since the purpose of this selection (i.e. a composition suitable for patient self-titration to effect) was not contemplated in the prior art.

Applicant has amended claim 29 to clarify the ambit of protection sought, and to change claim dependency. No new matter has been added by this amendment.

Claims 30-36 are dependent on claim 29. As such, since claim 29 is not obvious (for reasons stated above), it follows that claims 30-36 can not be obvious.

Applicant has also added new claim 48, to any combination of two different opioids, plus a pharmaceutically acceptable excipient suitable pulmonary administration, wherein the ratio of the two opioids in the formulation is selected such that the

combined pharmacokinetic profile of the opioids has a combined effect curve substantially similar to that shown in Figure 18. Support for this claim can be found throughout the application, for example at paragraph 0163, and elsewhere. Applicant submits that nothing in the prior art even contemplated pulmonary administration of two different opioids, much less in a ratio enabling patients to self-administer and titrate the opioids administered to effect, and, as such, claim 48 is neither obvious nor anticipated.

Double Patenting

The Examiner has rejected claims 1 and 5-18 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 10-25 of US patent No. RE38407.

Applicant has cancelled claims 1 and 5-16, rendering this objection, in regard to those claims, moot. Applicant reserves the right to re-introduce these claims, for example, in a divisional application.

With respect to claim 17, Applicant respectfully traverses. Applicant submits that claim 7 as presently amended is unobvious in light of RE38407, for the reasons submitted above. Note that RE38407 and the Mezei reference cited, referred to, and distinguished above have identical disclosures.

With respect to claim 18, as this claim is now dependent on claim 17, for the reasons stated above, Applicant submits the Examiner's rejection is moot.

The Examiner has provisionally rejected claims 1, 5-11, 13-21, 29-30 and 33 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 48 of copending application No. 10/927,145. Applicant respectfully requests this rejection be held in abeyance until the claims of the

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present patent application, or of copending application No. 10/927,145, are in a condition ready for allowance.

Conclusion

It is respectfully submitted that the present amendments and remarks herein are a complete response to all outstanding issues. Favorable consideration is respectfully requested. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

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